

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

## CERTIFICATE OF MAILING

I hereby certify that this Preliminary Amendment and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date indicated below the sufficient postage as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

  
Donald G. Lewis

Oct 30, 2001  
Date of Deposit

Applicant:	Boger	)	
		)	Art Unit: 1626
Serial No.:	unassigned	)	
		)	
Filed:	October 30, 2001	)	Examiner: Unassigned
		)	
For:	SYNTHESIS OF CC-1065/ DUOCARMYCIN ANALOGS	)	Our Ref.: TSRI 626.1 Div I
		)	

## PRELIMINARY AMENDMENT

Assistant Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

Filed herewith is a divisional application claiming priority from SN 09/581,049. Prior to examination of the enclosed divisional application, please amend the specification and claims as follows:

## AMENDMENTS

### In the Specification:

At page 1, line 1 of the specification, please insert the following new sentence:

### Statement of Government Support:

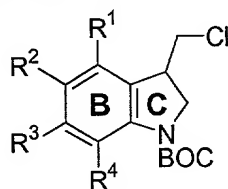
This invention was made with government support under Contract No. CA55276 by the National Institutes of Health. The government has certain rights in the invention.

In the Claims:

Please cancel claims 2-18 without prejudice.

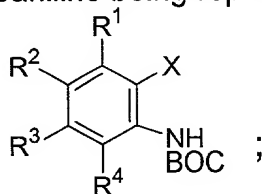
Please amend Claim 1 and add new claims 19-31 as follows:

1. (once amended) A process for synthesizing a dihydroindole C-ring of a CC-1065/duocarmycin analog, the dihydroindole C-ring of a CC-1065/duocarmycin analog being represented by the following structure:



the process comprising the following steps:

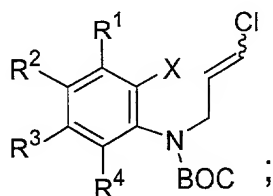
Step A: allylating an *ortho*-haloaniline with 1,3-dichloropropene for forming a vinyl chloride, the *ortho*-haloaniline being represented by the following structure:



wherein:

$R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  are radicals independently selected from the group consisting of hydrogen, alkyl(C1-C6), alkoxy, and arylalkoxy, with a proviso that  $R^1$  and  $R^2$ , or  $R^2$  and  $R^3$  may form a fused 5- or 6-membered ring with or without a heteroatom; and

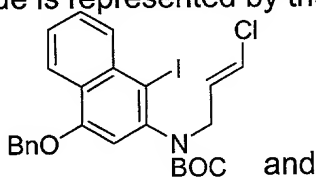
$X$  is a halide selected from the group consisting of bromine and iodine; and the vinyl chloride is represented by the following structure:



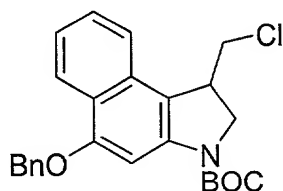
then

Step B: cyclizing the vinyl chloride of said step A for forming the dihydroindole C-ring of the CC-1065 / duocarmycin analog.

19. (new claim) A process according to claim 1 wherein, in said Step A, the *ortho*-haloaniline is an *ortho*-bromoaniline.
20. (new claim) A process according to claim 1 wherein, in said Step A, the *ortho*-haloaniline is an *ortho*-iodoaniline.
21. (new claim) A process according to claim 1 wherein, in said Step A, the *ortho*-haloaniline is protected with a BOC group.
22. (new claim) A process according to claim 1 wherein, in said Step A, said allylation is catalyzed by the addition of a catalytic amount of tetra-*n*-butyl ammonium iodide.
23. (new claim) A process according to claim 1 wherein, in said Step B, said cyclization is performed with an addition of tri-*n*-butyltin hydride.
24. (new claim) A process according to claim 23 wherein, in said Step B, said cyclization is catalyzed by the addition of a catalytic amount of AIBN.
25. (new claim) A process according to claim 24 wherein, in said Step B, said cyclization is performed using toluene as the solvent.
26. (new claim) A process according to claim 1 wherein:  
in said Step A, the vinyl chloride is represented by the following structure:

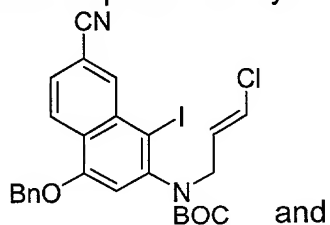


in said Step B, the dihydroindole C-ring of the CC-1065 / duocarmycin analog is represented by the following structure:

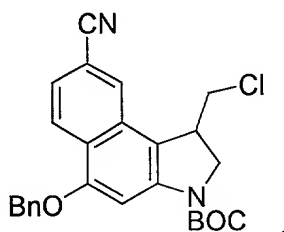


27. (new claim) A process according to claim 1 wherein:

in said Step A, the vinyl chloride is represented by the following structure:

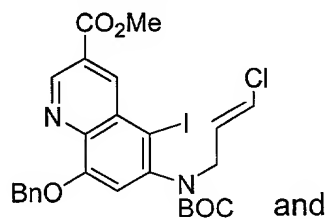


in said Step B, the dihydroindole C-ring of the CC-1065 / duocarmycin analog is represented by the following structure:

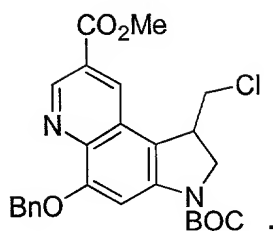


28. (new claim) A process according to claim 1 wherein:

in said Step A, the vinyl chloride is represented by the following structure:

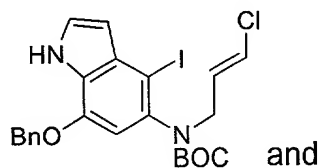


in said Step B, the dihydroindole C-ring of the CC-1065 / duocarmycin analog is represented by the following structure:

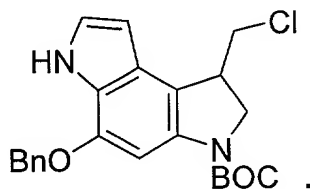


29. (new claim) A process according to claim 1 wherein:

in said Step A, the vinyl chloride is represented by the following structure:

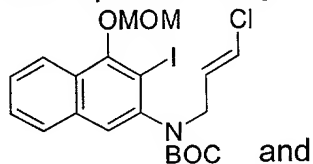


in said Step B, the dihydroindole C-ring of the CC-1065 / duocarmycin analog is represented by the following structure:

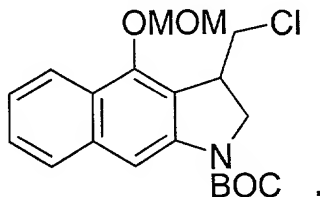


30. (new claim) A process according to claim 1 wherein:

in said Step A, the vinyl chloride is represented by the following structure:

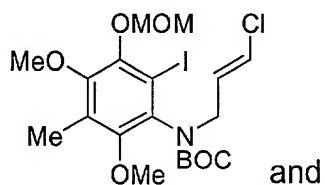


in said Step B, the dihydroindole C-ring of the CC-1065 / duocarmycin analog is represented by the following structure:

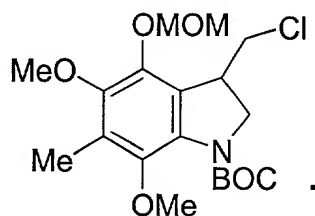


31. (new claim) A process according to claim 1 wherein:

in said Step A, the vinyl chloride is represented by the following structure:



in said Step B, the dihydroindole C-ring of the CC-1065 / duocarmycin analog is represented by the following structure:



Respectfully submitted,

Oct 30, 2001  
Date

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Donald G. Lewis, Reg. No. 28,636

THE SCRIPPS RESEARCH INSTITUTE

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October 30, 2001

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## APPENDIX

VERSION OF SPECIFICATION AND CLAIMS  
WITH MARKINGS TO SHOW CHANGES MADEIn the Specification:

At page 1, line 1 of the specification, please insert the following new sentence:

5      Statement of Government Support:

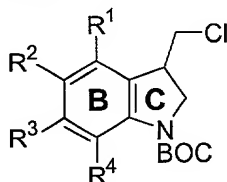
This invention was made with government support under Contract No. CA55276 by the National Institutes of Health. The government has certain rights in the invention.

10     In the Claims:

Please cancel claims 2-18 without prejudice.

Please amend Claim 1 and add new claims 19-31 as follows:

- 15     1. (once amended) A [method] process for [the synthesis] synthesizing a dihydroindole C-ring of a CC-1065/duocarmycin analog, the dihydroindole C-ring of a CC-1065/duocarmycin analog being represented by the following structure:



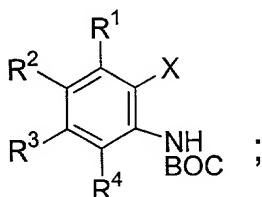
20

[wherein the method comprises] the process comprising the following steps [of]:

Step A: allylating an [aryl halide] ortho-haloaniline with 1,3-dichloropropene [and a catalytic amount of *n*-tetrabutylammonium iodide] for forming a vinyl chloride, the ortho-haloaniline being represented by the following structure:

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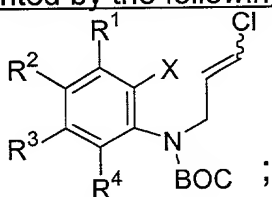
## APPENDIX

VERSION OF SPECIFICATION AND CLAIMS  
WITH MARKINGS TO SHOW CHANGES MADE

5 wherein:

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are radicals independently selected from the group consisting of hydrogen, alkyl(C1-C6), alkoxy, and arylalkoxy, with a proviso that R<sup>1</sup> and R<sup>2</sup>, or R<sup>2</sup> and R<sup>3</sup> may form a fused 5- or 6-membered ring with or without a heteroatom; and

10 X is a halide selected from the group consisting of bromine and iodine; and the vinyl chloride is represented by the following structure:



15 then

Step B: cyclizing the vinyl chloride of said step A [under conditions using tributyltin hydride, catalytic AIBN and toluene as the solvent] for forming the dihydroindole C-ring of the CC-1065 / duocarmycin analog.

20 19. (new claim) A process according to claim 1 wherein, in said Step A, the *ortho*-haloaniline is an *ortho*-bromoaniline.

20. (new claim) A process according to claim 1 wherein, in said Step A, the *ortho*-haloaniline is an *ortho*-iodoaniline.

25 21. (new claim) A process according to claim 1 wherein, in said Step A, the *ortho*-haloaniline is protected with a BOC group.



## APPENDIX

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WITH MARKINGS TO SHOW CHANGES MADE

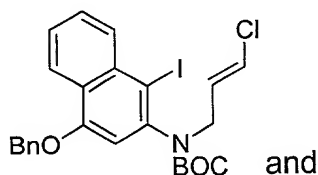
22. (new claim) A process according to claim 1 wherein, in said Step A, said allylation is catalyzed by the addition of a catalytic amount of tetra-*n*-butyl ammonium iodide.

23. (new claim) A process according to claim 1 wherein, in said Step B, said cyclization is performed with an addition of tri-*n*-butyltin hydride.

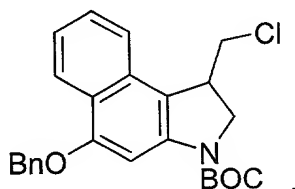
24. (new claim) A process according to claim 23 wherein, in said Step B, said cyclization is catalyzed by the addition of a catalytic amount of AIBN.

25. (new claim) A process according to claim 24 wherein, in said Step B, said cyclization is performed using toluene as the solvent.

26. (new claim) A process according to claim 1 wherein:  
in said Step A, the vinyl chloride is represented by the following structure:



in said Step B, the dihydroindole C-ring of the CC-1065 / duocarmycin analog is represented by the following structure:

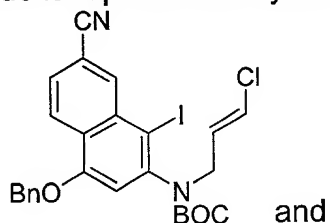


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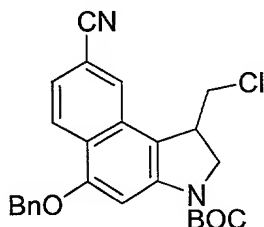
VERSION OF SPECIFICATION AND CLAIMS  
WITH MARKINGS TO SHOW CHANGES MADE

27. (new claim) A process according to claim 1 wherein:

in said Step A, the vinyl chloride is represented by the following structure:

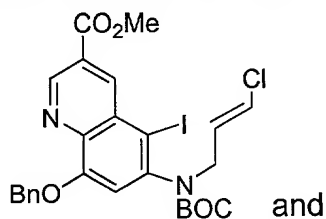


in said Step B, the dihydroindole C-ring of the CC-1065 / duocarmycin analog is represented by the following structure:

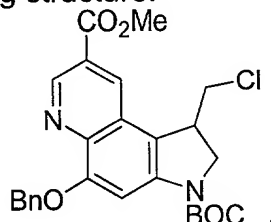


28. (new claim) A process according to claim 1 wherein:

in said Step A, the vinyl chloride is represented by the following structure:



in said Step B, the dihydroindole C-ring of the CC-1065 / duocarmycin analog is represented by the following structure:

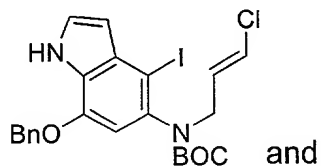


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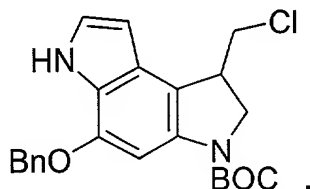
VERSION OF SPECIFICATION AND CLAIMS  
WITH MARKINGS TO SHOW CHANGES MADE

29. (new claim) A process according to claim 1 wherein:

in said Step A, the vinyl chloride is represented by the following structure:

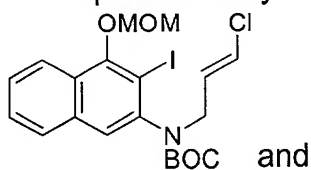


in said Step B, the dihydroindole C-ring of the CC-1065 / duocarmycin analog is represented by the following structure:

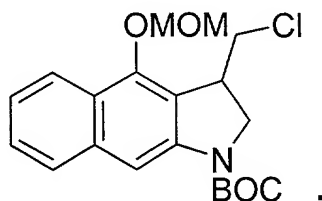


30. (new claim) A process according to claim 1 wherein:

in said Step A, the vinyl chloride is represented by the following structure:



in said Step B, the dihydroindole C-ring of the CC-1065 / duocarmycin analog is represented by the following structure:

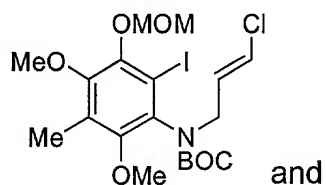


## APPENDIX

VERSION OF SPECIFICATION AND CLAIMS  
WITH MARKINGS TO SHOW CHANGES MADE

31. (new claim) A process according to claim 1 wherein:

in said Step A, the vinyl chloride is represented by the following structure:



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in said Step B, the dihydroindole C-ring of the CC-1065 / duocarmycin analog is represented by the following structure:

